ACS Catalysis

Subscriber access provided by UNIVERSITY OF TOLEDO LIBRARIES

Article

Cupraelectro-Catalyzed Alkyne Annulation: Evidence for Distinct C–H Alkynylation and Decarboxylative C–H/C–C Manifolds

Cong Tian, Uttam Dhawa, Alexej Scheremetjew, and Lutz Ackermann

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b02348 • Publication Date (Web): 12 Jul 2019

Downloaded from pubs.acs.org on July 12, 2019

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Cupraelectro-Catalyzed Alkyne Annulation: Evidence for Distinct C–H Alkynylation and Decarboxylative C–H/C–C Manifolds

Cong Tian,‡ Uttam Dhawa,‡ Alexej Scheremetjew, and Lutz Ackermann*

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstraße 2, 37077, Göttingen (Germany).

Supporting Information Placeholder

ABSTRACT: Synthetically meaningful isoindolones were accessed by cupraelectro-catalyzed C–H activation with electricity as terminal oxidant. Thus, a versatile, inexpensive and non-toxic $Cu(OAc)_2$ catalyst enabled broadly applicable C–H/N–H functionalizations on electron-rich and electron-deficient benzamides with distinct functional group tolerance and resource-economy. Detailed mechanistic studies provided strong support for a C–H alkynylation mechanism through fast C–H metalation, which likewise set the stage for cupraelectro-catalyzed C–H/C–C functionalizations in a decarboxylative fashion.

Keywords: alkynylation, annulation, copper, C–H activation, C–C cleavage, electrochemistry, isoindolone

INTRODUCTION

The effective conversion of renewable electricity into value-added chemical products bears considerable potential towards a sustainable energy economy.[1] C–H activation has emerged as an increasing powerful platform for molecular syntheses,[2] with transformative applications to late-stage diversification,[3] material sciences,[4a,b] and pharmaceutical industries.[4c,d] In recent years, merging oxidative C–H transformations with electrocatalysis[5] has significantly improved the sustainability of 3d-transition metal-catalyzed C–H activation,[6] hence avoiding the use of toxic and expensive stoichiometric oxidants. Thus, very recent momentum was gained by electrocatalysis for *inter alia* C–C,[7] C–O,[8] and C–N[9] bond formations,[10] with key contribution by Xu,[11] and Mei,[12] among others. In this context, Mei elegantly developed very recent copper-catalyzed electrochemical aminations with electron-rich anilides, through a proposed single electron transfer (SET) from the anilide substrates.[13] Despite indisputable advances, electrocatalyzed C–H alkynylations[14] have thus far generally proven elusive, while cupraelectro-catalyzed C–H activations of electron-deficient arenes are as of yet unprecedented. In sharp contrast, within our program on sustainable C–H activation,[15] we have now developed the first copper-catalyzed electro-oxidative alkyne annulation enabled by C–H alkynylations of synthetically-valuable, inherently electron-deficient aromatic amides (Figure 1). Notable features of our findings comprise 1) unprecedented electro-oxidative annulations by C–H alkynylations, 2) earth-abundant, non-toxic copper catalysts, 3) user-friendly undivided cell set-up, 4) mechanistic insights into cupraelectro-catalyzed C–H alkynylations, and 5) decarboxylative C–H/C–C functionalizations by electro-catalysis. It is noteworthy that in contrast to recent alkyne annulations for six-membered isoquinolones,[16] the metallaelectro-catalyzed C–H alkynylation delivered for the first time bioactive five-membered isoindolones.[17]

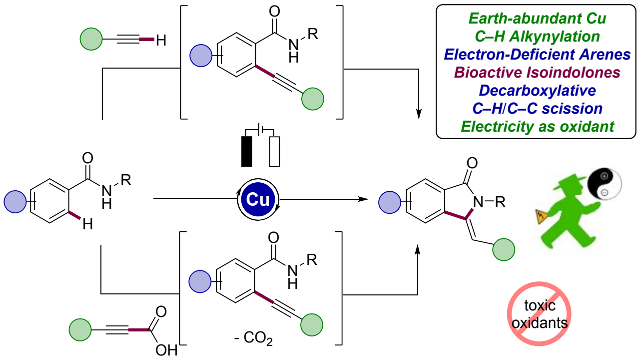


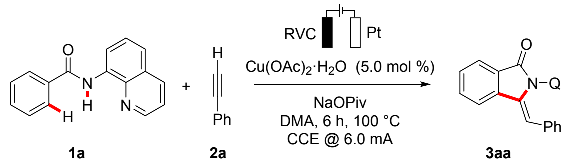
Figure 1. Cupraelectro-catalyzed C–H alkynylation.

RESULTS AND DISCUSSION

Optimization Studies. We initiated our studies by probing various reaction conditions for the envisioned copper-catalyzed electrooxidative C–H/N–H activation of benzamide **1a** with terminal alkyne **2a** in an operationally-simple undivided cell set-up (Table 1 and Table S1 in the Supporting Information). After considerable preliminary experimentation, we observed that the desired isoindolone **3aa** was obtained by catalytic amounts of $Cu(OAc)_2 \cdot H_2O$, along with NaOPiv as the optimal additive at 100 °C in DMA (entries 1-7). The addition of redox mediators, such as TBAI and TEMPO, did not improve the performance of the copper catalyst (entries 8-9). A reaction conducted in a potentiostatic manifold at 2.0 V gave similar results as was obtained for the galvanostatic regime (entry 10).

Control experiments revealed the essential role of the electricity, the additive and the copper catalyst with a minor influence of oxygen (entries 11-14). Notably, a set of typical transition metal catalysts based on manganese, nickel, ruthenium, rhodium, iridium and palladium fell short in delivering any products (entries 15-20).

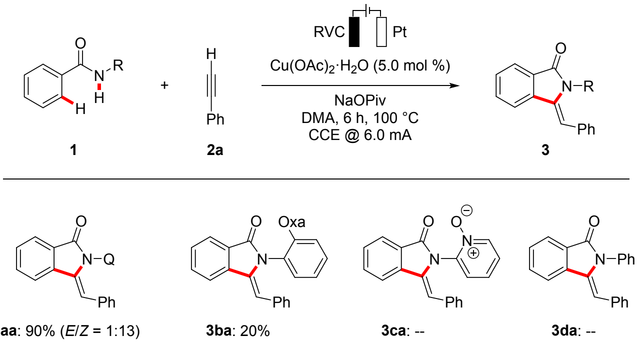
Table 1. Optimization of cupraelectro-catalyzed isoindolone synthesis.[a]



entry	deviation from standard condition	*E*/*Z*	yield [%][b]
1	**None**	**1:13**	**90**
2	NaOAc instead of NaOPiv	1:6	58
3	Na_2CO_3 instead of NaOPiv	1:4	44
4	KOPiv instead of NaOPiv	1:1	51
5	*t*AmOH instead of DMA	–	–
6	DMF instead of DMA	1:3	56
7	NMP instead of DMA	1:8	80
8	TBAI (50 mol %) additive	1:10	76
9	TEMPO (20 mol %) additive	1:8	81
10	Constant potential at 2.0 V	1:12	86
11	No electricity	1:8	18
12	No electricity, under N_2	1:9	5
13	No Cu catalyst	–	–
14	No NaOPiv	–	–
15	$Mn(OAc)_2$ as catalyst	–	–
16	$Ni(OAc)_2·4H_2O$ as catalyst	–	–
17	$[RuCl_2(p\text{-cymene})]_2$ as catalyst	–	–
18	$[Cp^*RhCl_2]_2$ as catalyst	–	–
19	$[Cp^*IrCl_2]_2$ as catalyst	–	–
20	$Pd(OAc)_2$ as catalyst	–	–

[a] General reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), $Cu(OAc)_2·H_2O$ (5.0 mol %), NaOPiv (1.0 equiv), DMA (4.0 mL), 100 °C, constant current at 6.0 mA, 6 h, RVC anode, Pt-plate cathode, undivided cell. [b] Yield of isolated product. DMA = *N,N*-Dimethylacetamide, DMF = *N,N*-Dimethylformamide, NMP = *N*-Methyl-2-pyrrolidone. TBAI = Tetra-*n*-butylammonium iodide.

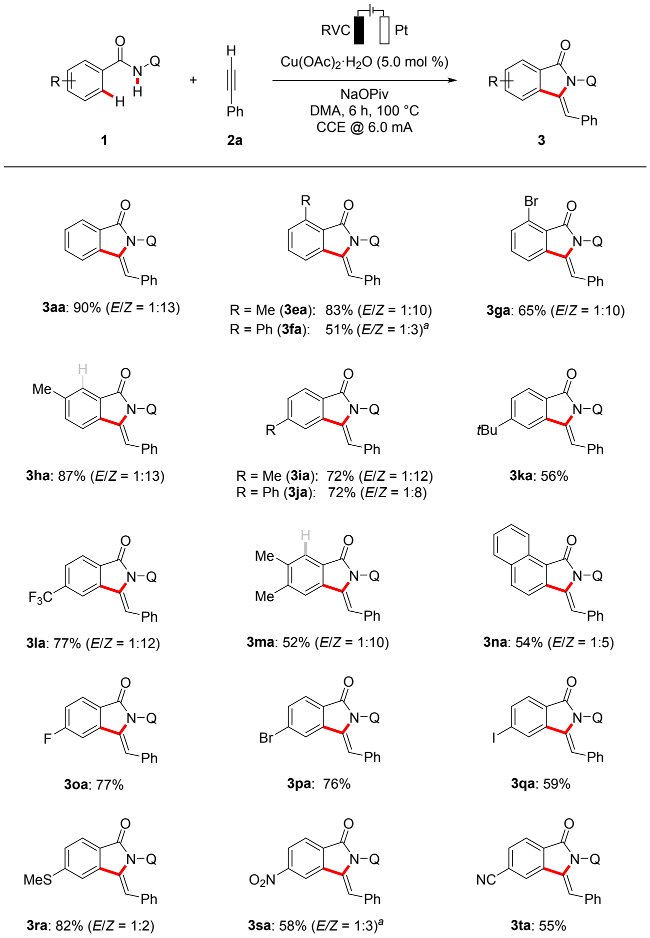
Subsequently, we evaluated the effect of the *N*-substitution-pattern on the cupraelectro-catalyzed C–H/N–H annulation (Scheme 1). Thus, either phenyl oxazoline **1b** or pyridine-*N*-oxide **1c** proved to be ineffective in giving comparable yields of the desired isoindolinone, as was also noted for the simple *N*-phenylbenzamide **1d**.



Oxa = 2-Oxazoline.

Scheme 1. Effect of the *N*-substitution on the cupraelectro-catalysis.

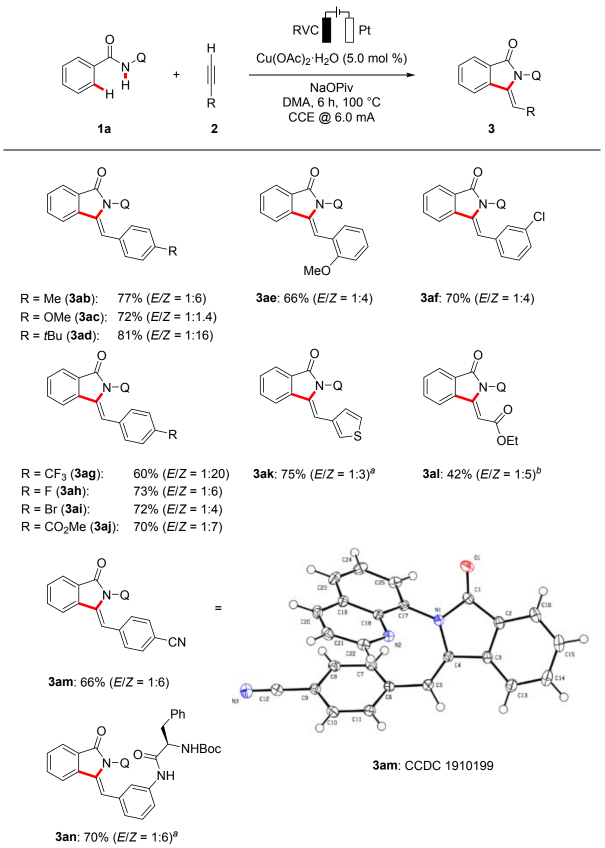
Versatility. With the optimized reaction conditions in hand, we tested the versatility of our cupraelectro-catalyzed annulation regime with diversely decorated benzamides **1** (Scheme 2). Electron-rich as well as electron-deficient arenes **1e**-**1n** were both amenable to the cupraelectro-catalyzed C–H alkynylation cascade, chemo-selectively providing the corresponding isoindolinones **3**. The positional selectivities for *meta*-substituted arenes **1h** and **1m** were governed by steric interactions. Notably, the sustainable copper catalyst tolerated a diverse array of valuable electrophilic functional groups, including thioether (**3ra**) and electron-withdrawing bromo (**3pa**), iodo (**3qa**), nitro (**3sa**) and cyano (**3ta**) substituents, which should prove invaluable for further late-stage diversifications.



[a] $Cu(OAc)_2 \cdot H_2O$ (10 mol %).

Scheme 2. Cupraelectro-catalyzed C–H alkynylation for isoindolones 3.

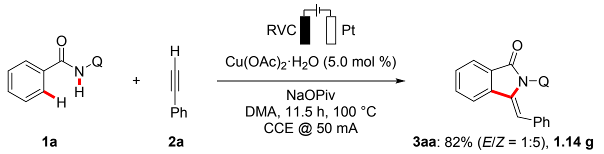
Likewise, we explored the versatility of amenable acetylenes **2** (Scheme 3). A wide variety of alkynes **2** with electron-donating and electron-withdrawing groups afforded the desired isoindolinones **3ab-3aj**. Generally, halo-substituents were well accepted under the optimized reaction condition. Gratifyingly, esters and cyanide groups-containing alkynes were chemo-selectively tolerated by the cupraelectro-annulation manifold. Notably, thiophene acetylene **2k** was also found to be suitable, efficiently furnishing the corresponding isoindolone **3ak**. It is noteworthy that the robustness of the copper-catalyzed C–H activation further allowed for excellent efficacy with the alkyne **2n** bearing an amino acid. The terminal alkynes with alkyl substituent lead to the oxygenation products in low yield instead of desired annulated products.



[a] $Cu(OAc)_2 \cdot H_2O$ (10 mol %). [b] $Cu(OAc)_2 \cdot H_2O$ (20 mol %).

Scheme 3. Cupraelectro-catalyzed C–H alkynylation cascade with alkyne 2.

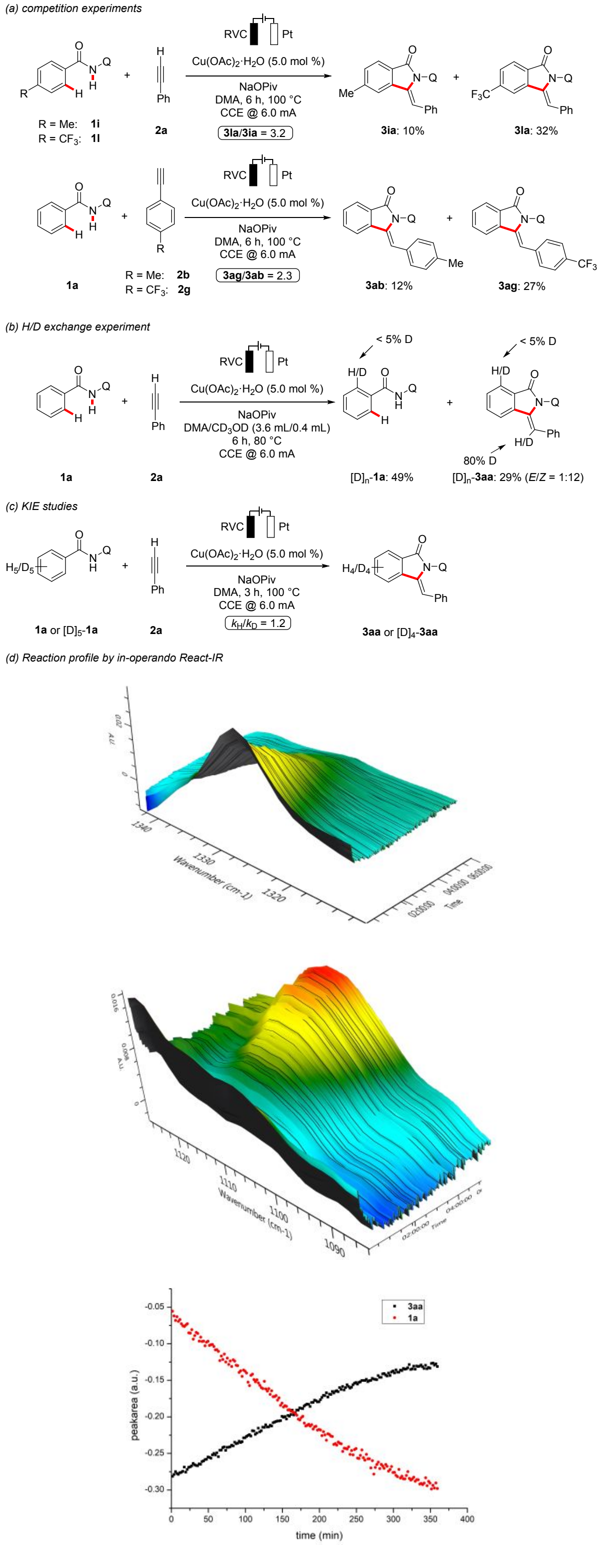
The user-friendly nature of the copper-catalyzed electrochemical C−H activation was reflected by the gram-scale synthesis of product **3aa**, which proceeded with high catalytic efficiency (Scheme 4).



Scheme 4. Gram-scale cupraelectro-catalyzed isoindolone synthesis.

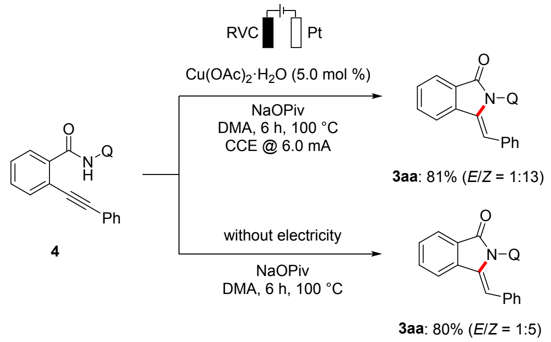
Mechanistic Studies. In consideration of the unique performance of the cupraelectro-catalyzed C–H activation, we became intrigued by probing the catalyst's mode of action. To this end, intermolecular competition experiments between different *para*-substituted benzamide **1** and alkyne **2** were conducted (Scheme 5a). Thus, the electron-withdrawing substrates **1l** and **2g** proved to be inherently superior,[18] which clearly highlights the complementary nature of our approach as compared to functionalization of electron-rich anilides by substrate SET-oxidation pathways.[9b, 13] Reactions conducted in the presence of isotopically-labeled CD_3OD as the cosolvent revealed the C–H cleavage not to be rate-determining (Scheme

5b). Kinetic isotope effect (KIE) studies performed by *in-operando* React-IR provided additional support for a facile C–H scission (Scheme 5c). Head-space gas-chromatographic analysis unraveled the formation of molecular hydrogen as the sole byproduct (Figure S5).



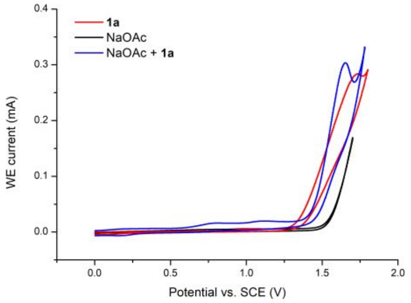
Scheme 5. Summary of key mechanistic findings.

Moreover, the independently prepared *ortho*-alkynylated substrate **4** successfully delivered the desired product **3aa** (Scheme 6), providing strong support for a C–H alkynylation regime.



Scheme 6. Support for C–H alkynylation pathway.

Furthermore, we conducted detailed cyclic voltammetry studies (Figure 2). In the presence of substrate **1a**, the copper(II) catalyst exhibited a pronounced oxidative current at 0.95 V *versus* SCE, while Cu(OAc)$_2$ itself did not reveal any relevant competitive oxidation peak. These findings are suggestive of the formation of a copper(II) complex **5**, which is in turn oxidized to a copper(III) intermediate. Subsequent C–H activation and reductive elimination give rise to a CuOAc species, which was shown to be easily reoxidized at 0.05 V *versus* SCE to generate the initial copper(II) salt. In the presence of substrate **1a**, CuOAc exhibited oxidative currents at both previously described potentials.



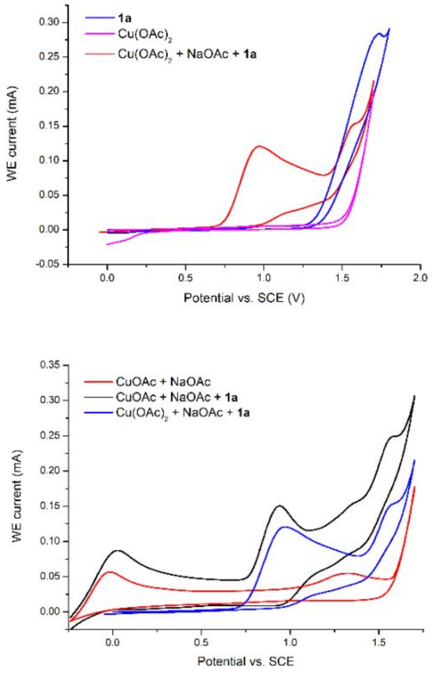
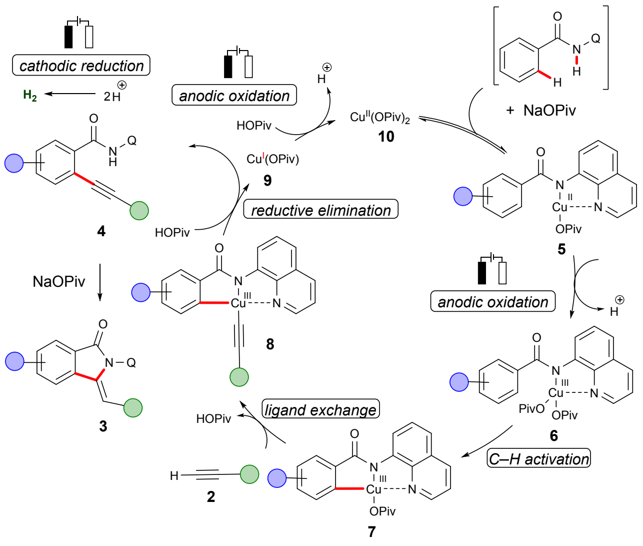


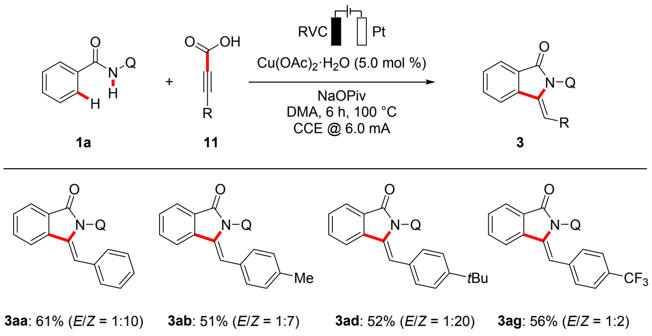
Figure 2. Cyclic voltammetry. General condition: DMA, 0.1 M $n\mathrm{Bu}_4\mathrm{NPF}_6$, 5 mM HOAc, 5 mM substrates, 100 mV/s.

Based on our detailed mechanistic studies, we propose a plausible catalytic cycle to commence by substrate coordination and subsequent anodic copper(II) oxidation, thus forming the catalytically competent copper(III) carboxylate species **6** (Scheme 7). Thereafter, facile carboxylate-assisted C–H activation on the electron-deficient benzamide generates the copper(III) intermediate **8**. Then, metalation of the terminal alkyne by carboxylate assistance, along with subsequent reductive elimination delivers the C–H alkynylated arene **4**, which was shown to undergo cyclization towards the desired isoindolone **3**. Finally, the copper(I) complex is oxidized at the anode by proton-coupled electron transfer to regenerate the catalytically active copper(III) species.



Scheme 7. Proposed catalytic cycle.

Decarboxylative C–H/C–C scission. Finally, the robustness of our cupraelectro-catalyzed C–H activation was mirrored by not being restricted to terminal alkynes **2**. Indeed, easily accessible alkynyl carboxylic acids **11** proved also applicable under otherwise identical reaction conditions, effectively providing the desired isoindolone **3** products by decarboxylative[19] C–H/C–C cleavage (Scheme 8).



Scheme 8. Decarboxylative cupraelectro-catalyzed C–H/C–C scission.

CONCLUSIONS

In conclusion, we have reported on the first electrooxidative cascade annulation by copper-catalyzed C–H alkynylation. Thus, a versatile cupraelectro-catalyzed domino regime featured excellent tolerance of synthetically useful functional groups and broad substrate scope, including electron-deficient benzamides. The cupraelectrocatalysis enabled sustainable C–H functionalization in the absence of toxic metal oxidants and generated molecular hydrogen as sole by-product. Detailed mechanistic studies provided strong support for an unprecedented C–H alkynylation by facile C–H activation, and set the stage for novel C–H/C–C functionalization in terms of decarboxylative metallaelectro-catalysis.

AUTHOR INFORMATION

Corresponding Author

*E-mail: Lutz.Ackermann@chemie.uni-goettingen.de

Author Contributions

‡C.T. and U.D. contributed equally to this work.

Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, compound characterization data (PDF)
Crystallographic data for $C_{25}H_{15}N_3O$ (CIF)

ACKNOWLEDGMENT

Generous support by the DFG (Gottfried-Wilhelm-Leibniz award), the CSC (Scholarship to C.T.) and the DAAD (fellowship to U.D.) is gratefully acknowledged. We thank Dr. Christopher Golz (Göttingen University) for the X-ray diffraction analysis.

REFERENCES

(1) Cook, T. R.; Dogutan, D. K.; Reece, S. Y.; Surendranath, Y.; Teets, T. S.; Nocera, D. G., Solar Energy Supply and Storage for the Legacy and Nonlegacy Worlds. *Chem. Rev.* **2010,** *110*, 6474-6502.

(2) For recent reviews, see: (a) Dey, A.; Sinha, S. K.; Achar, T. K.; Maiti, D. Accessing Remote *meta*- and *para*-C(sp^2)−H Bonds with Covalently Attached Directing Groups. *Angew. Chem. Int. Ed.* **2019**, *58*, 2-26. (b) Gandeepan, P.; Ackermann, L. Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis. *Chem* **2018**, *4*, 199-222. (c) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247-9301. (d) Ma, W.; Gandeepan, P.; Li, J.; Ackermann, L. Recent Advances in Positional-selective Alkenylations: Removable Guidance for Twofold C–H Activation. *Org. Chem. Front.* **2017**, *4*, 1435-1467. (e) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C–H Bonds. *Chem. Rev.* **2017**, *117*, 8754-8786. (f) Dey, A.; Maity, S.; Maiti, D. Reaching the South: Metal-catalyzed Transformation of the Aromatic *para*-Position. *Chem. Commun.* **2016**, *52*, 12398-12414. (g) McCann, S. D.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidations of Organic Molecules: Pathways for Two-Electron Oxidation with a Four-Electron Oxidant and a One-Electron Redox-Active Catalyst. *Acc. Chem. Res.* **2015**, *48*, 1756-1766. (h) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053-1064. (i) Wencel-Delord, J.; Glorius, F. C–H Bond Activation Enables the Rapid Construction and Late-stage Diversification of Functional Molecules. *Nat. Chem.* **2013**, *5*, 369. (j) Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp^2)–H and C(sp^3)–H Bonds by Using Bidentate Directing Groups. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743. (k) Daugulis, O.; Do, H.-Q.; Shabashov, D. Palladium- and Copper-Catalyzed Arylation of Carbon−Hydrogen Bonds. *Acc. Chem. Res.* **2009**, *42*, 1074-1086. (l) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C–H Activation/C–C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115. (m) Ackermann, L.; Vicente, R.; Kapdi, A. R. Transition-Metal-Catalyzed Direct Arylation of (Hetero)Arenes by C–H Bond Cleavage. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826.

(3) (a) Wang, W.; Lorion, M. M.; Shah, J.; Kapdi, A. R.; Ackermann, L. Late-Stage Peptide Diversification by Position-Selective C−H Activation. *Angew. Chem. Int. Ed.* **2018**, *57*, 14700-14717. (b) Noisier, A. F. M.; Brimble, M. A. C–H Functionalization in the Synthesis of Amino Acids and Peptides. *Chem. Rev.* **2014**, *114*, 8775-8806.

(4) (a) Pouliot, J.-R.; Grenier, F.; Blaskovits, J. T.; Beaupré, S.; Leclerc, M. Direct (Hetero)arylation Polymerization: Simplicity for Conjugated Polymer Synthesis. *Chem. Rev.* **2016**, *116*, 14225-14274. (b) Schipper, D. J.; Fagnou, K. Direct Arylation as a Synthetic Tool for the Synthesis of Thiophene-Based Organic Electronic Materials. *Chem. Mater.* **2011**, *23*, 1594-1600. (c) Seki, M. A New Catalytic System for Ru-Catalyzed C–H Arylation Reactions and Its Application in the Practical Syntheses of Pharmaceutical Agents. *Org. Process Res. Dev.* **2016**, *20*, 867-877. (d) Ackermann, L. Robust Ruthenium(II)-Catalyzed C–H Arylations: Carboxylate Assistance for the Efficient Synthesis of Angiotensin-II-Receptor Blockers. *Org. Process Res. Dev.* **2015**, *19*, 260-269.

(5) For recent reviews, see: (a) Meyer, T. H.; Finger, L. H.; Gandeepan, P.; Ackermann, L. Resource Economy by Metallaelectrocatalysis: Merging Electrochemistry and C–H Activation. *Trends Chem.* **2019**, *1*, 63-76. (b) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemistry: Calling All Engineers. *Angew. Chem. Int. Ed.* **2018**, *57*, 4149-4155. (c) Wiebe, A.; Gieshoff, T.; Mohle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S. R. Electrifying Organic Synthesis. *Angew. Chem. Int. Ed.* **2018**, *57*, 5594-5619. (d) Waldvogel, S. R.; Lips, S.; Selt, M.; Riehl, B.; Kampf, C. J. Electrochemical Arylation Reaction. *Chem. Rev.* **2018**, *118*, 6706-6765. (e) Tang, S.; Liu, Y.; Lei, A. Electrochemical Oxidative Cross-coupling with Hydrogen Evolution: A Green and Sustainable Way for Bond Formation. *Chem* **2018**, *4*, 27-45. (f) Sauermann, N.; Meyer, T. H.; Qiu, Y.; Ackermann, L. Electrocatalytic C–H Activation. *ACS Catal.* **2018**, *8*, 7086-7103. (g) Sauermann, N.; Meyer, T. H.; Ackermann, L. Electrochemical Cobalt-Catalyzed C−H Activation. *Chem. Eur. J.* **2018**, *24*, 16209-16217. (h) Mohle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angew. Chem. Int. Ed.* **2018**, *57*, 6018-6041. (i) Moeller, K. D. Using Physical Organic Chemistry To Shape the Course of Electrochemical Reactions. *Chem. Rev.* **2018**, *118*, 4817-4833. (j) Kärkäs, M. D. Electrochemical Strategies for C–H Functionalization and C–N Bond Formation. *Chem. Soc. Rev.* **2018**, *47*, 5786-5865. (k) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230-13319. (l) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008**, *108*, 2265-2299. (m) Jutand, A. Contribution of Electrochemistry to Organometallic Catalysis. *Chem. Rev.* **2008**, *108*, 2300-2347.

(6) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C–H Activation. *Chem. Rev.* **2019**, *119*, 2192-2452.

(7) (a) Yang, Q.-L.; Li, C.-Z.; Zhang, L.-W.; Li, Y.-Y.; Tong, X.; Wu, X.-Y.; Mei, T.-S. Palladium-Catalyzed Electrochemical C–H Alkylation of Arenes. *Organometallics* **2019**, *38*, 1208-1212. (b) Sau, S. C.; Mei, R.; Struwe, J.; Ackermann, L. Cobaltaelectro-Catalyzed C–H Activation with Carbon Monoxide or Isocyanides. *ChemSusChem*, **2019**, *12*, 3023-3027. (c) Qiu, Y.; Scheremetjew, A.; Ackermann, L. Electro-Oxidative C–C Alkenylation by Rhodium(III) Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 2731-2738. (d) Luo, M.-J.; Hu, M.; Song, R.-J.; He, D.-L.; Li, J.-H. Ruthenium(II)-catalyzed Electrooxidative [4+2] Annulation of Benzylic Alcohols with Internal Alkynes: Entry to Isocoumarins. *Chem. Commun.* **2019**, *55*, 1124-1127. (e) Kong, W.-J.; Finger, L. H.; de Oliveira, J. C. A.; Ackermann, L. Rhodaelectrocatalysis for Annulative C–H Activation: Polycyclic Aromatic Hydrocarbons by Versatile Double Electrocatalysis. *Angew. Chem. Int. Ed.* **2019**, *58*, 6342-6346. (f) Zeng, L.; Li, H.; Tang, S.; Gao, X.; Deng, Y.; Zhang, G.; Pao, C.-W.; Chen, J.-L.; Lee, J.-F.; Lei, A. Cobalt-Catalyzed Electrochemical Oxidative C–H/N–H Carbonylation with Hydrogen Evolution. *ACS Catal.* **2018**, *8*, 5448-5453. (g) Xu, F.; Li, Y.-J.; Huang, C.; Xu, H.-C. Ruthenium-Catalyzed Electrochemical Dehydrogenative Alkyne Annulation. *ACS Catal.* **2018**, *8*, 3820-3824. (h) Tang, S.; Wang, D.; Liu, Y.; Zeng, L.; Lei, A. Cobalt-catalyzed Electrooxidative C–H/N–H [4+2] Annulation with Ethylene or Ethyne. *Nat. Commun.* **2018**, *9*, 798. (i) Qiu, Y.; Tian, C.; Massignan, L.; Rogge, T.; Ackermann, L. Electrooxidative Ruthenium-Catalyzed C−H/O−H Annulation by Weak O-Coordination. *Angew. Chem. Int. Ed.* **2018**, *57*, 5818-5822. (j) Qiu, Y.; Stangier, M.; Meyer, T. H.; Oliveira, J. C. A.; Ackermann, L. Iridium-Catalyzed Electrooxidative C−H Activation by Chemoselective Redox-Catalyst Cooperation. *Angew. Chem. Int. Ed.* **2018**, *57*, 14179-14183. (k) Qiu, Y.; Kong, W.-J.; Struwe, J.; Sauermann, N.; Rogge, T.; Scheremetjew, A.; Ackermann, L. Electrooxidative Rhodium-Catalyzed C−H/C−H Activation: Electricity as Oxidant for Cross-Dehydrogenative Alkenylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 5828-5832. (l) Meyer, T. H.; Oliveira, J. C. A.; Sau, S. C.; Ang, N. W. J.; Ackermann, L. Electrooxidative Allene Annulations by Mild Cobalt-Catalyzed C–H Activation. *ACS Catal.* **2018**, *8*, 9140-9147. (m) Mei, R.; Koeller, J.; Ackermann, L. Electrochemical Ruthenium-catalyzed Alkyne Annulations by C–H/Het–H Activation of Aryl Carbamates or Ohenols in Protic Media. *Chem. Commun.* **2018**, *54*, 12879-12882. (n) Ma, C.; Zhao, C.-Q.; Li, Y.-Q.; Zhang, L.-P.; Xu, X.-T.; Zhang, K.; Mei, T.-S. Palladium-catalyzed C–H Activation/C–C Cross-coupling Reactions via Electrochemistry. *Chem. Commun.* **2017**, *53*, 12189-12192. (o) Saito, F.; Aiso, H.; Kochi, T.; Kakiuchi, F. Palladium-Catalyzed Regioselective Homocoupling of Arenes Using Anodic Oxidation: Formal Electrolysis of Aromatic Carbon–Hydrogen Bonds.

Organometallics **2014**, *33*, 6704-6707. (p) Amatore, C.; Cammoun, C.; Jutand, A. Electrochemical Recycling of Benzoquinone in the Pd/Benzoquinone-Catalyzed Heck-Type Reactions from Arenes. *Adv. Synth. Catal.* **2007**, *349*, 292-296, and cited references.

(8) (a) Tian, C.; Dhawa, U.; Struwe, J.; Ackermann, L. Cobaltaelectro-Catalyzed C–H Acyloxylation. *Chin. J. Chem.* **2019**, *37*, 552-556. (b) Shrestha, A.; Lee, M.; Dunn, A. L.; Sanford, M. S. Palladium-Catalyzed C–H Bond Acetoxylation via Electrochemical Oxidation. *Org. Lett.* **2018**, *20*, 204-207. (c) Yang, Q.-L.; Li, Y.-Q.; Ma, C.; Fang, P.; Zhang, X.-J.; Mei, T.-S. Palladium-Catalyzed C(sp^3)–H Oxygenation via Electrochemical Oxidation. *J. Am. Chem. Soc.* **2017**, *139*, 3293-3298. (d) Sauermann, N.; Meyer, T. H.; Tian, C.; Ackermann, L. Electrochemical Cobalt-Catalyzed C–H Oxygenation at Room Temperature. *J. Am. Chem. Soc.* **2017**, *139*, 18452-18455. (e) Li, Y.-Q.; Yang, Q.-L.; Fang, P.; Mei, T.-S.; Zhang, D. Palladium-Catalyzed C(sp^2)–H Acetoxylation via Electrochemical Oxidation. *Org. Lett.* **2017**, *19*, 2905-2908.

(9) (a) Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.; deGruyter, J. N.; Nakamura, H.; Knouse, K.; Qin, C.; Clay, K. J.; Bao, D.; Li, C.; Starr, J. T.; Garcia-Irizarry, C.; Sach, N.; White, H. S.; Neurock, M.; Minteer, S. D.; Baran, P. S. Electrochemically Driven, Ni-Catalyzed Aryl Amination: Scope, Mechanism, and Applications. *J. Am. Chem. Soc.* **2019**, *141*, 6392-6402. (b) Kathiravan, S.; Suriyanarayanan, S.; Nicholls, I. A. Electrooxidative Amination of sp^2 C–H Bonds: Coupling of Amines with Aryl Amides via Copper Catalysis. *Org. Lett.* **2019**, *21*, 1968-1972. (c) Zhang, S.-K.; Samanta, R. C.; Sauermann, N.; Ackermann, L. Nickel-Catalyzed Electrooxidative C−H Amination: Support for Nickel(IV). *Chem. Eur. J.* **2018**, *24*, 19166-19170. (d) Sauermann, N.; Mei, R.; Ackermann, L. Electrochemical C−H Amination by Cobalt Catalysis in a Renewable Solvent. *Angew. Chem. Int. Ed.* **2018**, *57*, 5090-5094. (e) Gao, X.; Wang, P.; Zeng, L.; Tang, S.; Lei, A. Cobalt(II)-Catalyzed Electrooxidative C–H Amination of Arenes with Alkylamines. *J. Am. Chem. Soc.* **2018**, *140*, 4195-4199.

(10) (a) Aiso, H.; Kochi, T.; Mutsutani, H.; Tanabe, T.; Nishiyama, S.; Kakiuchi, F. Catalytic Electrochemical C–H Iodination and One-Pot Arylation by ON/OFF Switching of Electric Current. *J. Org. Chem.* **2012**, *77*, 7718-7724. (b) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. Palladium-Catalyzed Aromatic C−H Halogenation with Hydrogen Halides by Means of Electrochemical Oxidation. *J. Am. Chem. Soc.* **2009**, *131*, 11310-11311.

(11) Hou, Z.-W.; Mao, Z.-Y.; Xu, H.-C. Recent Progress on the Synthesis of (Aza)indoles through Oxidative Alkyne Annulation Reactions. *Synlett* **2017**, *28*, 1867-1872.

(12) Ma, C.; Fang, P.; Mei, T.-S. Recent Advances in C–H Functionalization Using Electrochemical Transition Metal Catalysis. *ACS Catal.* **2018**, *8*, 7179-7189.

(13) Yang, Q.-L.; Wang, X.-Y.; Lu, J.-Y.; Zhang, L.-P.; Fang, P.; Mei, T.-S. Copper-Catalyzed Electrochemical C–H Amination of Arenes with Secondary Amines. *J. Am. Chem. Soc.* **2018**, *140*, 11487-11494.

(14) (a) Lee, W.-C. C.; Wang, W.; Li, J. J. Copper(II)-Mediated ortho-Selective C(sp^2)–H Tandem Alkynylation/Annulation and ortho-Hydroxylation of Anilides with 2-Aminophenyl-1*H*-pyrazole as a Directing Group. *J. Org. Chem.* **2018,** *83*, 2382-2388. (b) Zheng, X.-X.; Du, C.; Zhao, X.-M.; Zhu, X.; Suo, J.-F.; Hao, X.-Q.; Niu, J.-L.; Song, M.-P. Ni(II)-Catalyzed C(sp^2)–H Alkynylation/Annulation with Terminal Alkynes under an Oxygen Atmosphere: A One-Pot Approach to 3-Methyleneisoindolin-1-one. *J. Org. Chem.* **2016,** *81*, 4002-4011. (c) Hao, X.-Q.; Du, C.; Zhu, X.; Li, P.-X.; Zhang, J.-H.; Niu, J.-L.; Song, M.-P. Cobalt(II)-Catalyzed Decarboxylative C–H Activation/Annulation Cascades: Regioselective Access to Isoquinolones and Isoindolinones. *Org. Lett.* **2016,** *18*, 3610-3613. (d) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. Cobalt-Catalyzed Cyclization of Aliphatic Amides and Terminal Alkynes with Silver-Cocatalyst. *J. Am. Chem. Soc.* **2015**, *137*, 12990-12996. (e) Zhu, W.; Wang, B.; Zhou, S.; Liu, H. The Facile Construction of the Phthalazin-1(2*H*)-one Scaffold via Copper-mediated C–H(sp^2)/C–H(sp) Coupling under Mild Conditions. *Beilstein J. Org. Chem.* **2015,** *11*, 1624-1631. (f) Zhang, Y.; Wang, Q.; Yu, H.; Huang, Y. Directed Arene/Alkyne Annulation Reactions *via* Aerobic Copper Catalysis. *Org. Biomol. Chem.* **2014,** *12*, 8844-8850. (g) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. Cu(II)-Mediated Ortho C–H Alkynylation of (Hetero)Arenes with Terminal Alkynes. *J. Am. Chem. Soc.* **2014**, *136*, 11590-11593. (h) Dong, J.; Wang, F.; You, J. Copper-Mediated Tandem Oxidative C(sp^2)–H/C(sp)–H Alkynylation and Annulation of Arenes with Terminal Alkynes. *Org. Lett.* **2014**, *16*, 2884-2887. (i) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidative C–H Functionalizations: Trends and Mechanistic Insights. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062-11087. (j) Kulkarni, A. A.; Daugulis, O. Direct Conversion of Carbon-Hydrogen into Carbon-Carbon Bonds by First-Row Transition-Metal Catalysis. *Synthesis* **2009**, 4087-4109.

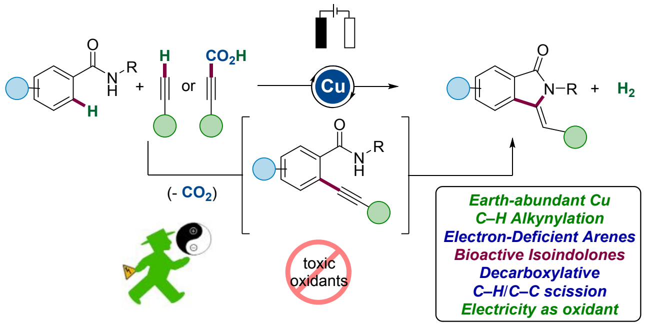
(15) (a) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C–H/Het–H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281-295. (b) Ackermann, L. Catalytic Arylations with Challenging Substrates: From Air-Stable HASPO Preligands to Indole Syntheses and C-H-Bond Functionalizations. *Synlett* **2007**, 507-526.

(16) (a) Tian, C.; Massignan, L.; Meyer, T. H.; Ackermann, L. Electrochemical C−H/N−H Activation by Water-Tolerant Cobalt Catalysis at Room Temperature. *Angew. Chem. Int. Ed.* **2018**, *57*, 2383-2387. (b) Mei, R.; Sauermann, N.; Oliveira, J. C. A.; Ackermann, L. Electroremovable Traceless Hydrazides for Cobalt-Catalyzed Electro-Oxidative C–H/N–H Activation with Internal Alkynes. *J. Am. Chem. Soc.* **2018**, *140*, 7913-7921.

(17) (a) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. A Concise First Total Aynthesis of Narceine Imide. *Org. Biomol. Chem.* **2007**, *5*, 1466-1471. (b) Kato, Y.; Ebiike, H.; Achiwa, K.; Ashizawa, N.; Kurihara, T.; Kobayashi, F. Synthesis and Inhibitory Activity of Isoindolinone Derivatives on Thromboxane A$_2$ Analog (U-46619)-Induced Vasocontraction. *Chem. Pharm. Bull.* **1990**, *38*, 2060-2062.

(18) (a) Davies, D. L.; Macgregor, S. A.; McMullin, C. L. Computational Studies of Carboxylate-Assisted C–H Activation and Functionalization at Group 8–10 Transition Metal Centers. *Chem. Rev.* **2017**, *117*, 8649-8709. (b) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C–H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315-1345.

(19) (a) Nairoukh, Z.; Cormier, M.; Marek, I. Merging C–H and C–C Bond Cleavage in Organic Synthesis. *Nat. Rev. Chem.* **2017**, *1*, 0035. (b) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies That Exploit C–C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017**, *117*, 9404-9432. (c) Pichette Drapeau, M.; Gooßen, L. J. Carboxylic Acids as Directing Groups for C−H Bond Functionalization. *Chem. Eur. J.* **2016**, *22*, 18654-18677. (d) Souillart, L.; Cramer, N. Catalytic C–C Bond Activations via Oxidative Addition to Transition Metals. *Chem. Rev.* **2015**, *115*, 9410-9464. (e) Xu, T.; Dermenci, A.; Dong, G. Transition Metal-Catalyzed C–C Bond Activation of Four-Membered Cyclic Ketones. *Top. Curr. Chem.* **2014**, *346*, 233-257, and cited references.


O
N
R
H
H
+
H
or
CO$_2$H
Cu
O
N–R
+
H$_2$
(- CO$_2$)
O
N
R
H
toxic oxidants
Earth-abundant Cu
C–H Alkynylation
Electron-Deficient Arenes
Bioactive Isoindolones
Decarboxylative
C–H/C–C scission
Electricity as oxidant